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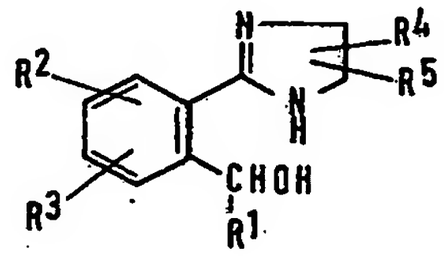
(54) NOVEL IMIDAZOLINE DERIVATIVES

(71) We, AMERICAN HOME PRODUCTS CORPORATION, a corporation organised and existing under the laws of the State of Delaware, United States of America, of 685 Third Avenue, New York 17, New York, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to α-aryl or heterocyclyl-*o* (2-imidazolinyl)benzyl alcohols which possess pharmacological activity, to processes for their preparation and to pharmaceutical compositions containing them.

The invention provides new compounds of general formula I



(I)

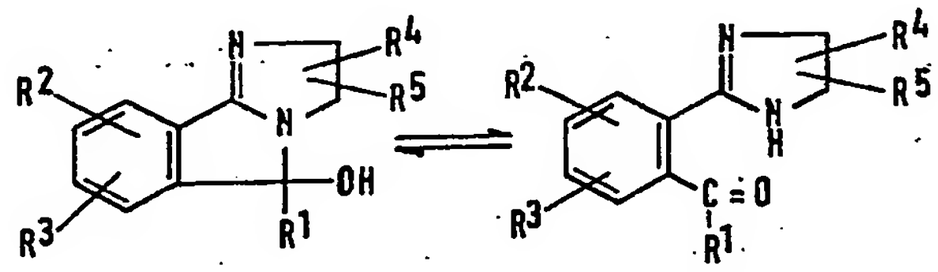
and their acid addition salts, wherein R^1 is phenyl, monohalophenyl dihalophenyl, mono(lower)alkylphenyl, di(lower)alkylphenyl, trifluoromethylphenyl, mono(lower)-alkoxyphenyl, di(lower)alkoxyphenyl, thienyl, pyridyl, furyl or 5,6,7,8-tetrahydro-2-naphthyl; R^2 is hydrogen, halogen, amino, (lower)alkylamino, (lower)alkyl or (lower)-alkoxy; R^3 is hydrogen when R^2 and R^3 are dissimilar and when R^2 and R^3 are the same they are both selected from hydrogen, halogen, (lower)alkyl and (lower)alkoxy; and R^4 and R^5 are both (lower)alkyl groups and both R^4 and R^5 are attached to the same carbon atom.

As employed herein the term "(lower)alkyl" is meant to include straight and branch chain hydrocarbon moieties of from 1 to 4 carbon atoms such as methyl, ethyl, propyl, *i*-propyl, and butyl. The t-butyl group is not contemplated within the scope of the term as used in this specification. The term "(lower)alkoxy" is used to include hydrocarbonyloxy groups which contain from 1 to 6 carbon atoms

[*Price 25p*]

such as methoxy, ethoxy, propoxy, butoxy and hexoxy. The terms "halogen" and "halo" as used herein are meant to include bromine, fluorine, chlorine and iodine.

The compounds of Formula I may be prepared by the reduction, e.g. with a hydride transfer agent such as a metal hydride or Meerwein-Ponndorf reagent, by catalytic hydrogenation with a mild catalyst, e.g. Raney nickel, or by a dissolving metal (nascent hydrogen), of the following compounds:

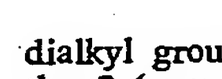


(II) (III)

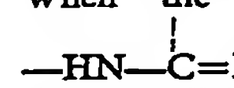
wherein R^1, R^2, R^3, R^4 and R^5 are the same as hereinbefore defined.

The preferred reducing agent is a complex metal hydride such as an alumino-hydride, or borohydride, e.g. lithium aluminium hydride, or sodium or potasium boro-hydride. An alkali metal hydride such as sodium hydride may also be employed. Suitable solvents for the reaction include anhydrous ether, tetrahydrofuran, diglyme and dioxane. The reduction is carried out by refluxing the reaction mixture for from 12 to 24 hours and subsequently adding water. Conventional techniques are thereafter employed to recover the product.

It has been found that the base form exists as the tricyclic imidazoisoindole form (II) and the acid-addition salt exists as the bicyclic phenyl ketone form (III). The nature of the reaction by which the compounds are prepared does not allow the position of the gemdialkyl groups to be fixed with certainty. When the compound exists as the phenyl ketone form, it is impossible to fix the position of the gem

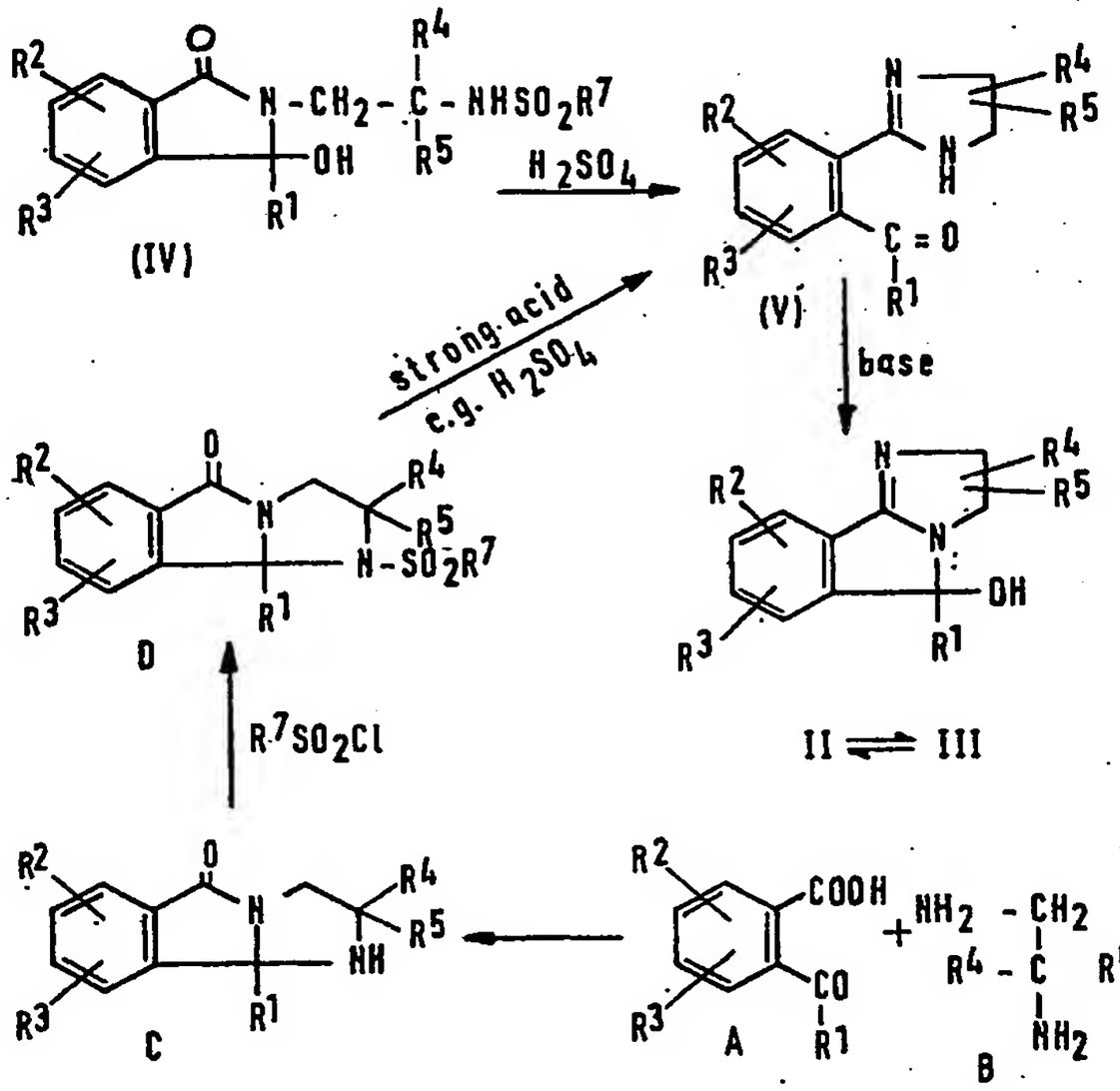


dialkyl groups because of the proton shift due to the —NH—C=N— group. Hence, the 2-(gem-dialkyl-2-imidazolin-2-yl)phenyl ketone acid-addition salts are named as 4,4(5,5)dialkyl-substituted compounds. This is in conformity with the nomenclature for imidazole type compounds set forth in Heterocyclic Compounds, R. C. Elderfield, Editor, Vol. 5, pp 198, 199 and 238, John Wiley and Sons, Inc., New York, 1957. When the imidazoisoindol-ol tautomer is formed, the tautomerism of the



—HN—C=N— moiety does not permit any absolute prediction as to positioning of the gem-dialkyl group. When the steric influence of the gem-dialkyl group is considered, the probability is great that the product obtained is a 2,2-dialkyl compound. Gas chromatographic studies indicate a single compound is isolated and not a mixture of the 2,2-dialkyl and 3,3-dialkyl isomers. As the available evidence does not conclusively eliminate the possibility of the formulation of the 3,3-dialkyl compound, the alternative nomenclature is employed herein, although it is believed that the structure is in actuality a 2,2-dialkyl-5*H*-imidazo[2,1-α]isoindol-5-ol.

The compounds of formulae II and III may be prepared by the following procedures:



wherein R^1, R^2, R^3, R^4 and R^5 are the same as herein above defined and R^7 is a hydrocarbon or substituted hydrocarbon group, e.g. (lower)alkyl, phenyl, monohalophenyl, dihalophenyl, mono(lower)alkylphenyl or di(lower)alkoxyphenyl (i.e. R^7SO_2— is an organosulphonyl residue whose nature is not critical).

The compounds of formula IV may be prepared by the sulphonylation of the phthalimidine compound C. The phthalimidines are readily prepared by reacting a Ψ-acid chloride of an *o*-aroyl-benzoic acid with the appropriate substituted or unsubstituted ethylene diamine compound. This type of compounds is described in the literature. (Sulkowski *et al* J. Org. Chem. *32*, 2180).

The preparation of related 5-aryl-2,3-dihydro-5*H*-imidazo[2,1-*a*]isoindol-5-ols is set forth in detail in British Patent Specification No. 1,229,652, which is incorporated herewith by reference.

The preparation of the 2-(gem-dialkyl-2-imidazolin-2-yl)phenyl ketone compounds is set forth in British Patent application No. 46940/70.

The compounds of the invention are useful anti-inflammatory agents which may be employed in comparative and experimental pharmacology as well as for other purposes. Those skilled in the art readily realise the desirability of employing control compounds which have demonstrated efficacy for inducing specific pharmacological effects when compounds of unknown activity are tested.

Activity of the compounds of the invention has been established by their ability to inhibit experimentally induced edema in the hind paw of the rat. Male Sprague-Dawley rats 120—160 grams are used. The compound is administered orally as a dispersion in distilled water (plus 2 drops of Tween 80) in a volume of 10 ml/kg. "Tween" is a registered Trade Mark. Compounds are given to 6 rats and the vehicle alone is administered to 6 more rats as a control. Sixty minutes later, drug administration edema is induced by an injection of 0.05 ml of a 1% carrageenin solution in physiological saline into the subplantar tissue of the rat's hind paw. Paw volume is then immediately measured volumetrically with a plethylsmograph and again 3 hours later. The new volume of swelling for the control group is

calculated and compared with that of the test group. Compounds that inhibit swelling approximately 23% in the test group subjects as compared with the controls are considered active. Inhibition is calculated by the formula:

$$\% \text{ Inhibition} = \frac{\text{Mean volume swelling of vehicle-treated subject} - \text{Mean volume swelling of compound-treated subject}}{\text{Mean volume swelling of vehicle-treated subject}} \times 100$$

The compounds of the invention are active anti-inflammatory agents when administered orally to mammals at dosages of from 10 to 100 milligrams per kilogram of body weight. The above test is an art recognised test for anti-inflammatory screening and evaluation. (Winter et al, Proc. Soc. Exp. Biol and Med. *111*: 544, 1962; Buttle et al, Nature *179*: 629, 1957).

The compounds of formula I provided by the invention contain basic nitrogen atoms and are capable of forming acid-addition salts with pharmaceutically acceptable acids, and the invention also provides such salts. Suitable acids for the formation of acid-addition salts include hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, acetic, lactic, citric, tartaric, maleic, gluconic, benzenesulphonic; toluenesulphonic, methylsulphonic and similar inorganic and organic acids.

The invention further provides a pharmaceutical composition which comprises a compound provided by the invention, which may, for example, be micronised, and a pharmaceutically acceptable non-toxic carrier.

Any suitable carrier known in the art can be used to prepare the pharmaceutical compositions. In such a composition, the carrier may be a solid, liquid or mixture of a solid and a liquid. Solid form compositions include powders, tablets and capsules. A solid carrier can be one or more substances which may also act as flavouring agents, lubricants, solubilisers, suspending agents, binders, or tablet-disintetgrating agents; it can also be an encapsulating material. In powders the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets the active ingredient is mixed with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from 5 to 99%, preferably 10—80%, by weight of the active ingredient. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low melting wax, and cocoa butter. The term "composition" is intended to include the formulation of an active ingredient with encapsulating material as carrier to give a capsule in which the active ingredient (with or without other carriers) is surrounded by carrier, which is thus in association with it. Similarly cachets are included.

Sterile liquid form compositions include sterile solutions, suspensions, emulsions, syrups and elixirs, The active ingredient can be dissolved or suspended in a pharmaceutically acceptable sterile liquid carrier, such as sterile water, a sterile organic solvent or a mixture of both. Preferably a liquid carrier is one suitable for parenteral injection. Where the active ingredient is sufficiently soluble it can be dissolved in normal saline as a carrier; if it is too insoluble for this it can often be dissolved in a suitable organic solvent, for instance aqueous propylene glycol or polyethylene glycol solutions. Aqueous propylene glycol containing from 10 to 75% of the glycol by weight is generally suitable. In other instances compositions can be made by dispersing the finely-divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution, or in a suitable oil, for instance arachis oil. Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilised by intramuscular, intraperitoneal or subcutaneous injection. In many instances a compound is orally active and can be administered orally either in lquid or solid composition form.

Preferably the pharmaceutical composition is in unit dosage form. In such form, the composition is sub-divided in unit doses containing appropriate quantities of the active ingredient; the unit dosage form can be a packaged composition, the package containing specific quantities of compositions, for example packeted powders or vials or ampoules. The unit dosage form can be a capsule, cachet or tablet itself, or it can be the appropriate number of any of these in packaged form. The quantity of active ingredient in a unit dose of composition may be varied or adjusted from 1 mg. or less to 500 mg. or more, according to the particular need and the activity of the active ingredient. The invention also includes the compounds in the absence of a carrier where the compounds are in unit dosage form.

When the compounds of the invention are employed as anti-inflammatory compounds, they may be administered to mammals, e.g. mice, rats, rabbits, dogs, cats and monkeys, alone or in combination with pharmacologically acceptable carriers, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration and standard biological practice. For example, they may be administered orally in the sold form containing such excipients as starch, milk, sugar and certain types of clay. The may also be administered orally in the form of solutions or they may be injected parenterally. For parenteral administration they may be used in the form of a sterile solution containing other solutes, for example, enough saline or glucose to make the solution isotonic.

The dosage of these compounds will vary with the form of administration and the particular compound chosen. Furthermore, it will very with the particular subject under treatment. Generally, treatment is initiated with small dosages substantially less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. In general, the compounds of this invention are most desirably administered at a concentration level that will generally afford effective results without causing any harmful or deleterious side effects.

The following examples are added to illustrate the invention:

EXAMPLE 1.

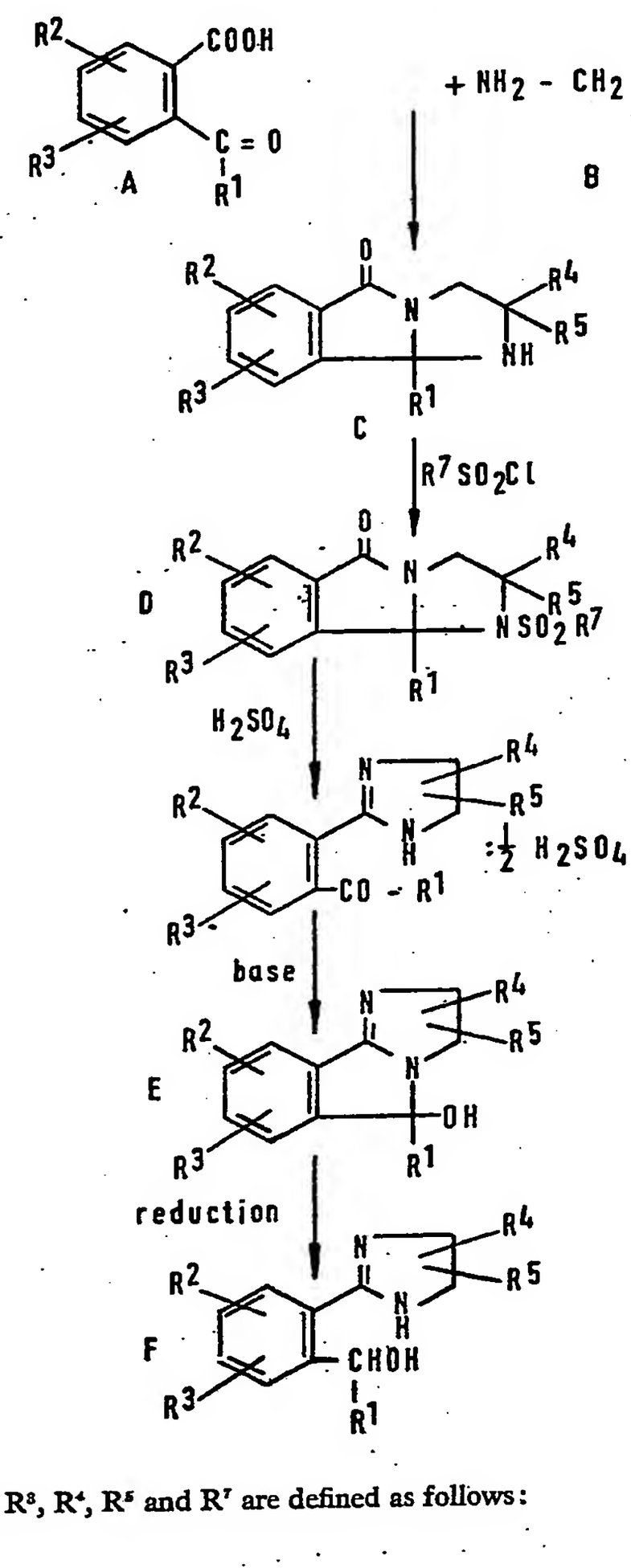
5-(*p*-chlorophenyl)-2,3-dihydro-2,2 (or 3,3)-dimethyl-5*H*-imidazo [2,1-*a*]isoindol-5-ol (28 g.) is added in portions to a suspension of 12 g. of lithium aluminium hydride in 500 ml. of anhydrous ether. The mixture is stirred and refluxed for 20 hours. The mixture is then decomposed by dropwise addition of water. The ether layer is separated and the filter cake is extracted with a total of 500 ml. of hot ethyl acetate. The organic extracts are combined and evaporated to dryness in vacuo. The residue is triturated with hexane to induce crystallization. The solid is separated and recrystallized from ethyl acetate to obtain 4′-chloro-2-[4,4 (5,5)-dimethyl-2-imidazolin-2-yl]benzhydrol, mp. 148—151°C.

Anal. Calcd for $C_{18}H_{19}ClN_2O$: C, 68.67; H. 6.08; N, 8.90; Cl, 11.27.
Found: C, 68.52; H, 6.28; N, 9.01; Cl, 11.33.

EXAMPLE 2.

A solution of 25 g. of the aroylbenzoic acid A, 75 ml. of toluene and 40 ml. of the gem-dialkyl-substituted 1,2-diaminopropane B is refluxed in a flask equipped with a water separator. After refluxing for 19 hours the solution is extracted with water, and then evaporated to dryness. The residue comprises the 9b-aryl-2,2-dialkyl-1,2,3,9b-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-one C as the major product. 38 g. of this product and 32 g. of *p*-toluenesulphonyl chloride in 125 ml. of pyridine solution are refluxed for 19 hours. The mixture is evaporated to dryness and the residue is dissolved in 100 ml. ethanol. After standing 18 hours the solid is collected and recrystallised to give the 9b-aryl-2,2-dialkyl-1,2,3,9b-tetrahydro-1-(*p*-tolylsulphonyl)-5*H*-imidazo[2,1-*a*]-isoindol-5-one D.

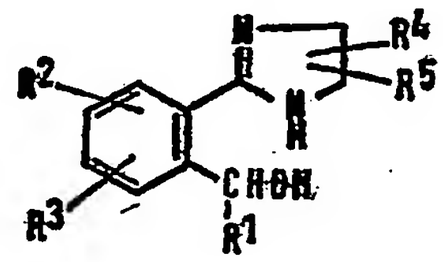
A solution of the last mentioned compound D, 25 g, in 90% sulphuric acid (100 ml.) is allowed to stand at room temperature for 45 minutes. The mixture is quenched with several volumes of ice-water and neutralised with concentrated sodium hydroxide solution. The solid is separate and washed with water and crystallised from a suitable crystallisation solvent, e.g. ethanol, to give the 5-aryl-2,3-dihydro-2,2 (3,3)-dialkyl-5*H*-imidazo[2,1-*a*]-isoindol-5-ol E. This compound in turn is reduced as in Example 1 to give the 2-[4,4 (or 5,5)-dialkyl-2-imidazolin-2-yl]benzhydrol derivative or analogue F. The representative values for R^1, R^2, R^3, R^4, R^5 and R^6 are given in the attached table. The following compounds are thereby prepared:



wherein R^1, R^2, R^3, R^4, R^5 and R^7 are defined as follows:

WHAT WE CLAIM IS:—

1. A compound having the general formula



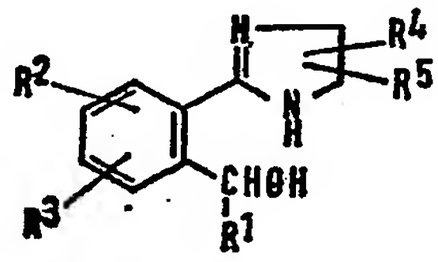
or its acid-addition salt; wherein R^1 is phenyl, monohalophenyl, dihalophenyl, mono(lower)alkylphenyl, di(lower)alkylphenyl, trifluoromethylphenyl, mono(lower)-alkoxyphenyl, di(lower)alkoxyphenyl, thienyl, pyridyl, furyl or 5,6,7,8-tetrahydro-2-naphthyl; R^2 is hydrogen, halogen, amino, (lower)alkylamino, (lower)alkyl or (lower)-alkoxy; R^3 is hydrogen when R^2 and R^3 are dissimilar and when R^2 and R^3 are the same they are both selected from hydrogen, halogen, (lower)alkyl and (lower)alkoxy; and R^4 and R^5 are both (lower)alkyl groups and both R^4 and R^5 are attached to the same carbon atom.

2. A compound according to Claim 1 in which R^4 and R^5 are both methyl groups.

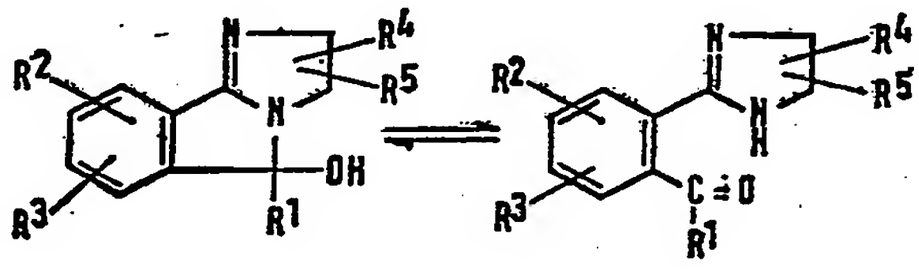
3. 4'-Chloro-2-[4,4 (or 5,5)-dimethyl-2-imidazolin-2-yl]-benzhydrol or an acid addition salt thereof.

4. A compound according to Claim 1 substantially as described herein with reference to the Examples.

5. A process for the preparation of a compound having the general formula



or its acid-addition salt wherein R^1, R^2, R^3, R^4 and R^5 are as defined in Claim 1, in which a compound having tautomeric forms represented by the following general formulae:



wherein R^1, R^2, R^3, R^4 and R^5 are as defined above, is reduced, and, if desired, a free base form of product is converted into its acid-addition salt.

6. A process according to Claim 5 in which the reduction is performed with a metal hydride.

7. A process according to Claim 5 in which the reduction is performed with an aluminohydride or a borohydride.

8. A process according to Claim 5 substantially as described herein with reference to the examples.

9. A compound prepared by a process according to any one of Claims 5 to 8.

10. A pharmaceutical composition comprising a compound according to any one of Claims 1 to 4 in association with a pharmaceutically acceptable carrier.

G. R. PORTER,
Agent for the Applicants,
John Wyeth & Brother Limited,
Huntercombe Lane South,
Taplow Maidenhead,
Berkshire.

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